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USSR WORK ON THE SYMBIOSIS OF VIRUSES AND MICROBES

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/Techniques described herein could conceivably be used in developing methods for biological warfare./

Symbiosis of viruses and microbes was studied in our laboratory during 1932 - 1937. The results of our investigations induced further work on the subject elsewhere. At present, a considerable amount of data in this field has been accumulated by us and other authors.

The results obtained in the course of this work suggest that viruses are not only adsorbed by bacteria and other microorganisms, but also multiply in the cells of the bacteria by which they are adsorbed. Experiments to verify this were carried out by us and other workers on viruses of vaccinia, smallpox of birds (Variola avium), measles, herpes, rabies, equine encephalomyelitis, swine cholera, and the foot and mouth disease.

We obtained symbiotic cultures of vaccinia and Torula kephir yeast, which retained their virus activity after being reseeded many times (one of them 120 times). These cultures can be used to infect rabbits and guinea pigs. Immunity to smallpox is established in these animals after the infection, but this immunity is not very strong or lasting. The virulence of vaccinia in yeast cultures drops after a while but can be restored by passing the virus through an animal. Cultures of this type were sent by us to the following institutes and were maintained by them: Central Institute imeni L. A. Tarasevich, the Central Institute of Epidemiology and Microbiology, and the Mechnikov Institute at Khar'kov.

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Similar experiments on vaccinia were conducted by other investigators (Ye. Gil'gut, 1935; M. Korol'kova, 1935; Izabolinskiy, Levtsov, and Chernyak, 1935; Timakov, 1935). Symbiotic cultures of this virus with staphylococci and sarcinae were obtained.

V. Tul'chinskaya (1936) developed cultures of Variola avium or Torula kephir which were active up to the 44th generation.

Work on artifical cultures of rabies with yeast did not lead to any positive results which could be confirmed, but some success was reported by at least one group (Rozengol'ts and Karnaukhova, 1934) in preparing a culture of rabies with Micr. lysodeicticus.

Of great interest is the work done by S. Minervin and Ye. Rapoport (1936) on symbiotic rabies bacteria cultures which develop under natural conditions. They cultivated on blood agar microorganisms obtained from the oral regions of dogs which died of rabies and infected rabbits subdurally with 5-10 bacterial bodies taken from the bouillon culture grown for 3-5 days (up to the 7th generation). After incubation, which continued for 9-60 days, the animals developed typical cases of experimental rabies. Furthermore, the disease could be passed repeatedly from one rabbit to another. The organs and blood of the diseased rabbits remained bacteriologically sterile. The investigators did not observe typical Negri bodies in the brains of the diseased animals, but established the presence of formations similar to these bodies. The best results in the experiments in question were obtained with a certain gram-positive bacillus and a streptococcus.

Symbiosis of the type encountered in the case of rabies virus does not necessarily imply complete preservation of all biological properties of the virus during symbiosis. The principal effect is apparently that the virus is preserved in a bacterial culture under conditions which would preclude its survival otherwise.

In the case of a virus like that of tick encephalitis, which affects the central nervous system and by-passes nonsterile organs and tissues of the animal organism, symbiosis is possible only with bacteria living in the body of the tick. It would be of interest to investigate the virus of tick encephalitis from this standpoint.

M. Grundfest (1934) obtained positive results with herpes-Torula kephir cultures.

Symbiotic cultures of the virus of hog cholera were studied by Likhachev (1937). Basing his work on the fact that enterococci and sarcinae are most often isolated from the blood of hogs suffering from cholera, Likhachev at-tempted to breed symbiotic cultures of the virus of hog cholera on these bacteria. He found that the fifth, tenth, and 21st generation of such cultures produced hog cholera in young pigs. Furthermore, the disease could be transmitted by injecting the blood of animals which had been infected into other animals, or by keeping healthy pigs next to the infected pigs. Immunity to hog cholera was not established by the injection of a 21st generation culture (the ninth and tenth generation were not tested as far as their power to confer immunity is concerned). Cultures of enterococci or sarcinae without hog cholera virus did not produce any pathological symptoms in young pigs.

Interesting results were obtained on symbiotic cultures of the virus of foot and mouth disease in work started as early as 1933 by L. A. Zil'ber and Ye. I. Vostrukhova. While attempts to breed symbiotic cultures of this virus on Torula kephir did not succeed, Ye. I. Vostrukhova was able to isolate from the paws of guinea pigs infected with foot and mouth disease a slowly growing

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streptococcus which definitely was established to be a virus carrier. The symbiotic culture on this streptococcus infected guinea pigs with foot and mouth disease up to the ninth generation of the culture. On the other hand, reseeding the virus without bacteria did not keep it alive later than the third generation. The work was not continued beyond this point, and the results were never published.

In 1936, in Germany, K. Poppe and G. Busch developed cultures of foot and mouth disease virus on several species of yeasts. The cultures prepared by them were reportedly active up to the 60th generation.

Although the causative factor of typhus is a rickettsia rather than an ultravirus, it behaves similarly to viruses in that it is a cell parasite and cannot propagate on artificial nutritive media. It also shares with ultraviruses the property of being adsorbed on microbes and entering into symbiosis with them. The fact that rickettsiae can exist only as cell parasites must have contributed to their adaptation as far as symbiosis with microbes invariably found in the intestine of lice is concerned. We, and later Minervin (1935), established that the causative factor of typhus forms symbiotic cultures with Proteus vulgaris (including Proteus X_{19}), and that it modifies the properties of Proteus. R. Gel'tser and S. Nemshilov (1934) cultivated the causative factor of typhus, obtained from the blood of diseased persons, on Sacharomyces cerevisae and Torula kephir. These symbiotic cultures proved to be suitable for the production of immune sera by the infection of horses, calves, or rams. Further results on symbiotic cultures of typhus rickettsia were obtained by A. Yakovlev (1934), G. Kalina and M. Danishevskaya (1933), K. Tokarevich and N. Klyacho (1935), Ye. Levkovich (1934), A. Afanas'yeva and N. Strekhova (1934), V. Elin, E. Frekman, and K. Urban (1935), M. Gnutenko and V. Friauf (1935), A. Kompaneyets, et al. (1936), S. Minervin, B. Zil'berman, and V. Gebril'skiy (1936), etc. These investigators used sarcinae; kephir, bread, and beer yeast; proteus; and bacteria isolated from the intestine of lice. Some of the results obtained by them were positive, and others were negative. Minervin and his group (1936) isolated from the intestine of lice taken from typhus patients bacterial cultures which produced typhus on being injected subcutaneously into guinea pigs. In some cases the disease could be passed through the brain of guinea pigs, while the brain remained bacteriologically sterile. Subsequently, Zil'berman and Gebril'skiy (1938) reported that the fourth and sixth generations of typhus rickettsiae cultures on bacteria isolated from the intestine of lice did not exhibit the presence of the causative factor of typhus when attempts were made to infect guinea pigs with these cultures. Zil'berman and Gebril'skiy's attempts to cultivate the causative factor of typhus on Proteus vulgaris, yeasts, and sarcinae were also unsuccessful according to their report. They found, furthermore, that some strains of Proteus vulgaris which had been in contact with the blood of typhus patients acquired the capacity of being agglutinated by the serum of rabbits immunized with X_{19}; also that the carrier microorganism alone, in some cases, produced pathogenic phenomena in guinea pigs.

In evaluating these results, one must realize that all authors who studied symbiotic cultures of typhus compared the properties of these cultures with those of a pure culture of the causative factor of typhus which had been thoroughly adapted to guinea pigs. Naturally, symbiotic cultures cannot be expected to exhibit to a full extent the properties of a pure culture. On the whole, it seems to be established that the carrier microorganisms are harmless, while their symbiotic cultures produced symptoms which are typical of typhus, [redacted] carrier bacteria would perish (for instance, on being kept for many months in a constant temperature closet).

The data cited above show convincingly that symbiosis between viruses and microbes exists. The phenomenon in question has been very aptly named virophoria. Data have been published by A. Yakovlev (1) and others which indicate that viruses survive in a medium populated by microbes without entering into any close contact with them. Apparently some microbes may produce substances which aid in the survival of viruses. Other types of symbiosis, besides virophoria, also probably exist. The similarity between virophoria and bacteriophagy is apparent: the bacteriophages, which are very similar to viruses, may have evolved from viruses existing in symbiosis with bacteria. This theory may be tested experimentally. If, for instance, we assume that typhoid bacteriophage has originated from a virophorous strain of an ancestor of the present typhoid bacillus which carried a virus having affinity to cells of the intestine, some of this affinity for intestinal cells must have been preserved in typhoid bacteriophage. A study of this and similar problems.may help in developing better methods for the use of bacteriophages in the prophylaxis and therapy of infectious diseases.

The following lines of investigation appear promising:

1. One should investigate the symbiosis of viruses with bacteria which occur together with them under natural conditions. Thus, one should study symbiosis of variola virus with bacteria of the skin and mucous membranes, of the virus of rabies with bacteria which occur in the saliva of dogs, of the virus of lymphogranulomatosis of the groin with skin bacteria, of the virus of influenza with bacteria of the mouth and nasopharynx, of the virus of tick encephalitis with bacteria infesting ticks, of the virus of Japanese encephalitis with bacteria of mosquitoes, etc.

2. One should study all forms of symbiosis rather than only propagation of viruses in symbiotic cultures. From the practical viewpoint, capacity of carrying the virus which is not necessarily accompanied by propagation of the virus in the microbial cell appears to be more important.

3. Virophoria as it occurs under natural conditions should be studied by isolating virophoric bacterial cultures from diseased tissues.

4. Particular attention should be paid to the preservation of the virus in virophoric cultures and conditions which contribute to this preservation.

5. The capacity of microbial cultures to become virophoric should be investigated under natural conditions, i.e., by introducing the microbial culture under investigation into the afflicted tissue and then isolating it from this tissue within a few days.

In studying virophoria, close attention should be paid to changes which the carrier microbe, as well as the virus, undergo in virophoric cultures. For instance, Meysel' (1936) observed a number of cytological changes to which yeast is subjected in virophoric cultures containing smallpox virus.

One must differentiate between pathogenic effects produced by the virus and those which are due to the carrier bacterium. For instance, when a virophoric culture of staphylococci which carry influenza virus is investigated, it should be tested on healthy mice, mice treated with anti-influenza virus serum, and mice treated with antistaphylococci serum.

[redacted]

viruses are preserved longer than in the absence of carrier microbes, a reservoir of pathogenic viruses is maintained by this means in nature. Symbiosis must be taken into consideration in clarifying the epidemiology of some virus diseases, e.g., poliomyelitis. Adsorption of viruses on bacteria is also of diagnostic importance. Thus, Sergieyev and his group (2), as well as others, have shown that bacteria, on adsorption of viruses, may be used for detecting antibodies to these viruses: agglutination of bacteria loaded with the virus in question takes place under the action of the antibodies.

A study of the symbiosis of viruses and microbes would tend to rectify the errors of investigators who, on isolating carrier microbes in virus diseases, assumed that the microbes in question are the causative factor of the disease. By looking at the photomicrographs with which G. Bosh'yan's book (3) is illustrated, one can readily see, to mention one instance, that the microorganisms referred to as a spherical modification of the causative factor of equine infectious anemia are actually yeast. Since yeast cannot produce the disease in question, one must assume that it acted in this case as a carrier of the virus of infectious anemia.

Phenomena of symbiosis do not comprise the whole range of relationships between viruses and microbes in nature: there may be also antagonism. The problem of antagonism acquires importance in connection with the recent discovery that the polysaccharides of some bacteria have an inhibiting action on the propagation of certain viruses. Further study of problems in this field, which were first formulated and investigated by USSR scientists, will enrich science with knowledge that is both of theoretical and practical significance.

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